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Assistent

Novel extracts or concentrates of Alpinia galanga or Languas galanga and pharmaceutical compositions containing them, the use of such extracts or concentrates for preparing certain medicaments, and a method of preparing an extract of Alpinia galanga or Languas galanga.

FIELD OF THE INVENTION

The present invention relates to the plant Alpinia galanga and more specifically to extracts or concentrates as well as pharmaceutical compositions derived from it. Furthermore the invention relates to the use of such extracts or concentrates for the preparation of medicaments for the treatment or prevention of hypersensitivity reactions and diseases associated with hypersensitivity reactions. The invention also relates to a method of preparing an extract of Alpinia galanga and to the extracts prepared by the method.

BACKGROUND OF THE INVENTION

Alpinia galanga (L.), family Zingiberaceae, commonly known as Greater Galangal or Java Galangal, is cultivated and grows wild in Asia. The herb is rhizomatic, 1.8 - 2.1 m in height with oblong glabrous leaves and greenish white flowers. The fruits are orange-red capsules.

The volatile oil can be obtained by steam distillation of the rhizome. It is a complex mixture with 1,8-cineol as the most abundant compound. Other major constituents are: α-pinene, β-pinene, limonene, α-terpineol, terpen-4-ol, and trans-β-farnesene.

A number of chemicals that are not volatile with steam have been identified as major compounds in extracts of the rhizome. The chemical composition of an extract depends on the choice of solvent, but in most cases 1'-acetoxychavicol acetate is the quantitatively dominating

compound. Other constituents are: 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol.

Primarily from the seeds of Alpinia galanga a few skeletal diterpenoids have been identified. Among these compounds are galangal A, galangal B, galanolactone, labda-8(17)-12-dien-15,16-dial and 8-17-epoxylabd-12-en-15,16-dial.

Hypersensitivity is defined as a state of altered reactivity in which the body reacts with an exaggerated immune response to a substance (antigen). Hypersensitivity may be caused by exogenous or endogenous antigens.

Hypersensitivity reactions underlie a large number of diseases. Amongst these allergic and autoimmune conditions are of great importance. A classification of hypersensitivity diseases is given by Parveen Kumar and Michael Clark in the textbook Clinical Medicine (3rd edition, 1994, p. 147-150, Baillière Tindall, London).

Type I hypersensitivity reactions (IgE mediated allergic reactions) are caused by allergens (specific exogenous antigens), e.g. pollen, house dust, animal dandruff, moulds, etc. Allergic diseases in which type I reactions play a significant role include asthma, eczema (atopic dermatitis), urticaria, allergic rhinitis and anaphylaxis.

Type II hypersensitivity reactions are caused by cell surface or tissue bound antibodies (IgG and IgM) and play a significant role in the pathogenesis of myasthenia gravis, Goodpasture's syndrome and Addisonian pernicious anaemia.

Type III hypersensitivity reactions (immune complex) are caused by autoantigens or exogenous antigens, such as certain bacteria, fungi and parasites. Diseases in which type III hypersensitivity reactions play a significant role include lupus erythematosus, rheumatoid arthritis and glomerulonephritis.

Type IV hypersensitivity reactions (delayed) are caused by cell or tissue bound antigens. This type of hypersensitivity plays a significant role in a number of conditions, e.g. graft-versus-host disease, leprosy, contact dermatitis and reactions due to insect bites.

A number of drug classes are available for the treatment of hypersensitivity reactions. Some of these are systemic and some are applied topically.

The corticosteroids are among the most widely used drugs for the treatment of hypersensitivity diseases. Corticosteroids primarily exert their pharmacological action by non-selectively inhibiting the function and proliferation of different classes of immune cells. Hereby hypersensitivity reactions are suppressed. Unfortunately the corticosteroids are associated with a number of serious side effects e.g. immuno-suppression, osteoporosis and skin atrophy (when applied topically).

SUMMARY OF THE INVENTION

We have found that extracts or concentrates of Alpinia galanga or Languas galanga significantly suppress hypersensitivity reactions. Compared to the corticosteroids extracts or concentrates of Alpinia galanga or Languas galanga have the advantage of not being associated with any serious side effects.

Due to their pharmacological effects extracts or concentrates of Alpinia galanga or Languas galanga can be employed for the following therapeutic applications:

- Immunomodulation.
- Treatment or prevention of hypersensitivity diseases.
- Treatment or prevention of IgE mediated allergic reactions and conditions.
- Treatment or prevention of autoimmune disorders.
- Alleviation of pain.

Accordingly the present invention provides a pharmaceutical composition containing extracts or concentrates of Alpinia galanga or Languas galanga and a pharmaceutically acceptable carrier.

More specifically the present invention provides the use of extracts or concentrates of Alpinia galanga or Languas galanga for preparing a medicament for immunomodulation, for the suppression of hypersensitivity reactions such as IgE mediated allergic reactions and autoimmune reactions, and for the alleviation of pain.

Thus, according to the invention extracts or concentrates of Alpinia galanga or Languas galanga can be used in a method for the treatment or prevention of a hypersensitivity disease in an individual, which comprises administering such plant material or a pharmaceutical composition containing it to said individual; and the invention comprises the use of extracts or concentrates of Alpinia galanga or Languas galanga for preparing a medicament for the treatment or prevention of hypersensitivity diseases.

Also, according to the invention extracts or concentrates of Alpinia galanga or Languas galanga can be used in a method for the treatment or prevention of an autoimmune

disorder in an individual, which comprises administering such plant material or a pharmaceutical composition containing it to said individual; and the invention comprises the use of extracts or concentrates of Alpinia galanga or Languas galanga for preparing a medicament for the treatment or prevention of autoimmune disorders.

Further, according to the invention extracts or concentrates of Alpinia galanga or Languas galanga can be used in a method for the treatment or prevention of an IgE mediated allergic reaction or condition in an individual, which comprises administering such plant material or a pharmaceutical composition containing it to said individual; and the invention comprises the use of extracts or concentrates of Alpinia galanga or Languas galanga for preparing a medicament for the treatment or prevention of IgE mediated allergic reactions and conditions.

Also, according to the invention extracts or concentrates of Alpinia galanga or Languas galanga can be used in a method for the alleviation of pain in an individual, which comprises administering such plant material or a pharmaceutical composition containing it to said individual; and the invention comprises the use of extracts or concentrates of Alpinia galanga or Languas galanga for preparing a medicament for the alleviation of pain.

Further, the invention provides a method of preparing an extract of Alpinia galanga, which comprises extracting said plant or parts thereof, preferably the rhizome, with an extraction agent comprising an organic solvent and subsequently, if necessary, removing the extraction agent to obtain an extract suitable for utilisation.

DETAILED DESCRIPTION OF THE INVENTION

Surprisingly it has been found that extracts or concentrates of Alpinia galanga or Languas galanga exert phar-

macological actions relevant to the therapeutic treatment of conditions associated with hypersensitivity reactions and pain.

More specifically extracts or concentrates of Alpinia galanga or Languas galanga provide the following pharmacological effects upon administration to the living organism:

- Immunomodulation.
- Suppression of hypersensitivity reactions.
- Suppression of IgE mediated allergic reactions.
- Suppression of autoimmune reactions.
- Reduction of pain.

Surprisingly according to the invention especially advantageous extracts or concentrates of Alpinia galanga or Languas galanga can be obtained with specific chemical compositions being new. These are superior to the plant it self or known components of the plant, when these are used alone (e.g. 1'-acetoxychavicol acetate). Furthermore the invention provides novel pharmaceutical or food preparations with specific chemical compositions.

Accordingly the present invention provides an extract or concentrate of Alpinia galanga or Languas galanga containing:

a) 2-99,5 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 0,5-98 % essential oil of Alpinia galanga or Languas galanga or mixtures thereof.

Thus preferably the present invention provides an extract or concentrate of Alpinia galanga or Languas galanga containing:

a) 5-99 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 1-95 % essential oil of Alpinia galanga or Languas galanga or mixtures thereof.

Even more preferably the present invention provides an extract or concentrate of Alpinia galanga or Languas galanga containing:

a) 10-98 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 2-90 % essential oil of Alpinia galanga or Languas galanga or mixtures thereof.

Furthermore the present invention provides an extract or concentrate of Alpinia galanga or Languas galanga containing:

a) 2-99,5 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-me-

thoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 0,5-98 % of one or more compounds selected from the group consisting of 1,8-cineol, α-pinene, β-pinene, limonene, α-terpineol, terpen-4-ol, and trans-β-farnesene.

Thus, preferably the present invention provides an extract or concentrate of Alpinia galanga or Languas galanga containing:

a) 5-99 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 1-95 % of one or more compounds selected from the group consisting of 1,8-cineol, α-pinene, β-pinene, limonene, α-terpineol, terpen-4-ol, and trans-β-farnesene.

Even more preferably the present invention provides an extract or concentrate of Alpinia galanga or Languas galanga containing:

a) 10-98 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 2-90 % of one or more compounds selected from the group consisting of 1,8-cineol, α-pinene, β-pinene, limonene, α-terpineol, terpen-4-ol, and trans-β-farnesene.

Also the present invention provides an extract or concentrate of Alpinia galanga or Languas galanga containing:

a) 2-99,5 % 1'-acetoxychavicol acetate;

b) 0,5-98 % of one or more compounds selected from the group consisting of 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol.

Thus, preferably the present invention provides an extract or concentrate of Alpinia galanga or Languas galanga containing:

a) 5-99 % 1'-acetoxychavicol acetate;

b) 1-95 % of one or more compounds selected from the group consisting of 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol.

Thus, preferably the present invention provides an extract or concentrate of Alpinia galanga or Languas galanga containing:

a) 10-98 % 1'-acetoxychavicol acetate;

b) 2-90 % of one or more compounds selected from the group consisting of 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol.

Furthermore the present invention provides a pharmaceutical or food composition comprising:

a) 0,01-99,9% of an extract or concentrate of Alpinia galanga or Languas galanga according to any one of claims 1-3;

b) 0,1-99,99% of a pharmaceutically acceptable vehicle.

Thus, preferably the present invention provides a pharmaceutical or food composition comprising:

a) 0,1-99% of an extract or concentrate of Alpinia galanga or Languas galanga according to any one of claims 1-3;
b) 1-99,9% of a pharmaceutically acceptable vehicle.

Even more preferably the present invention provides a pharmaceutical or food composition comprising:

a) 1-90% of an extract or concentrate of Alpinia galanga or Languas galanga according to any one of claims 1-3;
b) 10-99% of a pharmaceutically acceptable vehicle.

Also the present invention provides a pharmaceutical or food composition comprising:

a) 0,01-99,89 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;
b) 0,01-99,89 % essential oil of Alpinia galanga or Languas galanga or mixtures thereof;
c) 0,1-99,98 a pharmaceutically acceptable vehicle.

Thus, preferably the present invention provides a pharmaceutical or food composition comprising:

a) 0,1-98,9 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;
b) 0,1-98,9 % essential oil of Alpinia galanga or Languas galanga or mixtures thereof;
c) 1-99,8 a pharmaceutically acceptable vehicle.

Even more preferably the present invention provides a pharmaceutical or food composition comprising:

a) 1-89 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 1-89 % essential oil of Alpinia galanga or Languas galanga or mixtures thereof;

c) 10-98 a pharmaceutically acceptable vehicle.

Furthermore the present invention provides a pharmaceutical or food composition comprising:

a) 0,01-99,89 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 0,01-99,89 % of one or more compounds selected from the group consisting of 1,8-cineol, α-pinene, β-pinene, limonene, α-terpineol, terpen-4-ol, and trans-β-farnesene;

c) 0,1-99,98 % of a pharmaceutically acceptable vehicle.

Thus, preferably the present invention provides a pharmaceutical or food composition comprising:

a) 0,1-98,9 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 0,1-98,9 % of one or more compounds selected from the group consisting of 1,8-cineol, α-pinene, β-pinene, limonene, α-terpineol, terpen-4-ol, and trans-β-farnesene;
c) 1-99,8 % of a pharmaceutically acceptable vehicle.

Even more preferably the present invention provides a pharmaceutical or food composition comprising:
a) 1-89 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;
b) 1-89 % of one or more compounds selected from the group consisting of 1,8-cineol, α-pinene, β-pinene, limonene, α-terpineol, terpen-4-ol, and trans-β-farnesene;
c) 10-98 % of a pharmaceutically acceptable vehicle.

Also the present invention provides a pharmaceutical or food composition comprising:
a) 0,01-99,89 % 1'-acetoxychavicol acetate;
b) 0,01-99,89 % of one or more compounds selected from the group consisting of 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;
c) 0,1-99,98% of a pharmaceutically acceptable vehicle.

Thus, preferably the present invention provides a pharmaceutical or food composition comprising:
a) 0,1-98,9 % 1'-acetoxychavicol acetate;
b) 0,1-98,9 % of one or more compounds selected from the group consisting of 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-

hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamyl-alkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

c) 1-99,8% of a pharmaceutically acceptable vehicle.

Even more preferably the present invention provides a pharmaceutical or food composition comprising:

a) 1-89 % 1'-acetoxychavicol acetate;

b) 1-89 % of one or more compounds selected from the group consisting of 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamyl-alkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

c) 10-98% of a pharmaceutically acceptable vehicle.

Furthermore the present invention provides a pharmaceutical or food composition comprising:

a) 0,01-99,89% of Alpinia galanga or Languas galanga or parts, extracts or components thereof or an extract or concentrate thereof according to any one of claims 1-3;

b) 0,01-99,89% of Zingiber officinale or parts, extracts or components thereof;

c) 0,1-99,98% of a pharmaceutically acceptable vehicle.

Thus, preferably the present invention provides a pharmaceutical or food composition comprising:

a) 0,1-98,9% of Alpinia galanga or Languas galanga or parts, extracts or components thereof or an extract or concentrate thereof according to any one of claims 1-3;

b) 0,1-98,9% of Zingiber officinale or parts, extracts or components thereof;

c) 1-99,8% of a pharmaceutically acceptable vehicle.

Even more preferably the present invention provides a pharmaceutical or food composition comprising:

a) 1-89% of Alpinia galanga or Languas galanga or parts, extracts or components thereof or an extract or concentrate thereof according to any one of claims 1-3;
b) 1-89% of Zingiber officinale or parts, extracts or components thereof;
c) 10-98% of a pharmaceutically acceptable vehicle.

Also the present invention provides a pharmaceutical or food composition comprising:
a) 0,01-99,89% of Alpinia galanga or Languas galanga or parts, extracts or components thereof or an extract or concentrate thereof according to any one of claims 1-3;
b) 0,01-99,89% of γ-linolenic acid or eicosapentaenoic acid, optionally in the form of vegetable oil or fish oil;
c) 0,1-99,98% of a pharmaceutically acceptable vehicle.

Thus, preferably the present invention provides a pharmaceutical or food composition comprising:
a) 0,1-98,9% of Alpinia galanga or Languas galanga or parts, extracts or components thereof or an extract or concentrate thereof according to any one of claims 1-3;
b) 0,1-98,9% of γ-linolenic acid or eicosapentaenoic acid, optionally in the form of vegetable oil or fish oil;
c) 1-99,8% of a pharmaceutically acceptable vehicle.

Even more preferably the present invention provides a pharmaceutical or food composition comprising:
a) 1-89% of Alpinia galanga or Languas galanga or parts, extracts or components thereof or an extract or concentrate thereof according to any one of claims 1-3;
b) 1-89% of γ-linolenic acid or eicosapentaenoic acid, optionally in the form of vegetable oil or fish oil;
c) 10-98% of a pharmaceutically acceptable vehicle.

The above mentioned actions provide part of the rationale for the following therapeutic applications of Alpinia galanga or Languas galanga or extracts or concentrates thereof:

- A method for the treatment or prevention of hypersensitivity diseases characterised by the administration of extracts or concentrates of Alpinia galanga or Languas galanga. The therapeutic action may be relevant to all known diseases associated with hypersensitivity reactions. Below autoimmune disorders and IgE mediated allergic conditions are described more in detail. Besides these specific therapeutic areas the action of extracts or concentrates of Alpinia galanga or Languas galanga is relevant to all known conditions and diseases associated with hypersensitivity reactions and the following examples are not limiting with respect to this: infections (viral, bacterial, fungal, parasitic, etc.), cold and flu, contact dermatitis, insect bites, allergic vasculitis, postoperative reactions, transplantation rejection (graft-versus-host disease), etc.

- A method for the treatment or prevention of autoimmune disorders characterised by the administration of extracts or concentrates of Alpinia galanga or Languas galanga. The applicant puts forward the hypothesis that the therapeutic action is due to the immunomodulating and suppressing effect on hypersensitivity reactions of extracts or concentrates of Alpinia galanga or Languas galanga. The therapeutic action may be relevant to all known autoimmune disorders and the following examples are not limiting with respect to this: Autoimmune hepatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Autoimmune hemolytic anemias, Grave´s disease, Myasthenia gravis, Type 1 Diabetes Mellitus, Inflammatory myopathies, Multiple sclerosis, Hashimoto's thyreoiditis, Autoimmune adrenalitis, Crohn Disease, Ulcerative Colitis, Glomerulonephritis, Progressive

Systemic Sclerosis (Scleroderma), Sjögren's Disease, Lupus Erythematosus, Primary vasculitis, Reumatoid Arthritis, Juvenile Arthritis, Mixed Connective Tissue Disease, Psoriasis, Pemfigus, Pemfigoid, Dermatitis Herpetiformis, etc.

- A method for the treatment or prevention of IgE mediated allergic reactions and conditions characterised by the administration of extracts or concentrates of Alpinia galanga or Languas galanga. The applicant puts forward the hypothesis that the therapeutic action is due to the suppressing effect on hypersensitivity reactions of extracts or concentrates of Alpinia galanga or Languas galanga. The therapeutic action may be relevant to all known IgE mediated allergic reactions and conditions and the following examples are not limiting with respect to this: asthma, eczema (e.g. atopic dermatitis), urticaria, allergic rhinitis, anaphylaxis, etc.

- A method for the treatment or prevention of any condition associated with pain characterised by the administration of extracts or concentrates of Alpinia galanga or Languas galanga. The applicant puts forward the hypothesis that the therapeutic action is related to immunomodulation, possibly to suppressing effects on hypersensitivity reactions.

The preferred embodiment of the invention is an extract of Alpinia galanga. Extracts according to the invention can i.a. be obtained by extraction or distillation (e.g. hydro, steam or vacuum distillation) of fresh or dried Alpinia galanga or parts thereof, preferably the rhizome. Extraction may be performed with a number of different organic solvents and mixtures of water miscible solvents with water. The extraction can be performed hot or cold by the employment of any extraction technology e.g. maceration, percolation or supercritical extraction.

The preferred extraction solvents are acetone, methyl ethyl ketone, methyl acetate, ethyl acetate, lower alkanols having 1 to 4 carbon atoms, pentane, hexane or heptane. The preferred extraction temperature is close to the boiling point of the employed solvent due to extraction efficacy, but lower temperatures are also applicable making necessary a longer period of extraction.

By changing the composition of the applied solvent the extraction can be made more selective for certain constituents of Alpinia galanga thus enhancing or reducing their content in the finished extract.

After the primary extraction process a second step of processing, such as liquid-liquid extraction, column chromatography or any type of distillation, can be employed to remove or to concentrate and possibly isolate any constituent of the extract. Hereby any constituent of Alpinia galanga can be avoided or concentrated in the finished extract, e.g. 1,8-cineol, α-pinene, β-pinene, limonene, α-terpineol, terpen-4-ol, trans-β-farnesene, 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol, 3,4-dimethoxy-trans-cinnamylalkohol, galangal A, galangal B, galanolactone, labda-8(17)-12-dien-15,16-dial and 8-17-epoxylabd-12-en-15,16-dial. Thus the content of any component of Alpinia galanga can be standardised in the finished extract for the purpose of manufacturing a pharmaceutical composition.

According to the invention extracts or concentrates of Alpinia galanga or Languas galanga can be combined with any other active ingredient or plant extract to potentiate the therapeutic action. Consequently, we propose to combine Alpinia galanga or Languas galanga or extracts or concentrates thereof with eicosapentaenoic acid from fish

oils or γ-linolenic acid for any of the above mentioned therapeutic applications of Alpinia galanga or Languas galanga or extracts or concentrates thereof. As a parallel, we propose to combine Alpinia galanga or Languas galanga or extracts or concentrates thereof with Zingiber officinale or parts thereof or extracts or components thereof for the same therapeutic applications.

Furthermore it is obvious that in the use according to the invention for preparing medicaments extracts or concentrates of Alpinia galanga or Languas galanga may be mixed with additives such as surfactants, solvents, thickeners, stabilisers, preservatives, antioxidants, flavour etc. to obtain a desirable product formulation. Similarly, the pharmaceutical compositions according to the invention may further contain such additives. There are no limitations to the route of administration or dosage form of the formulation and the following examples are not limiting with respect to this: tablets, capsules, fluids, granulates, gels, ointments, emulsions (e.g. cremes and lotions), sprays (e.g. aerosol), eye drops, etc. Optionally, the composition may also contain surfactants such as bile salts, polyoxyethylene-sorbitan-fatty acid esters or polyalcohol mixed chain-length fatty acid esters for improving dispersibility of the composition in the digestive fluids leading to improved bioavailability or for obtaining the final dosage form of the composition.

EXAMPLES

Example 1

An extract of Alpinia galanga according to the invention was prepared as follows:

50 g dried root of Alpinia galanga was extracted with 500 ml of boiling methanol for 3 hours. This extraction was

repeated with the same starting material using again 500 ml methanol in 3 hours. Thereafter the extract was filtrated and evaporated to dryness under vacuum. Thus, 2.5 g of an amber-coloured liquid extract was obtained suitable for the manufacture of tablets, hard gelatine capsules, ointment, nasal drops, etc.

Example 2

An extract of Alpinia galanga according to the invention was prepared as follows:

50 g dried root of Alpinia galanga was extracted with 500 ml of boiling 50 % methanol for 3 hours. This extraction was repeated with the same starting material using again 500 ml ethanol in 3 hours. Thereafter the extract was filtrated and evaporated to dryness under vacuum. Thus, 2.8 g of an amber-coloured liquid extract was obtained suitable for the manufacture of tablets, hard gelatine capsules, ointment, nasal drops, etc.

Example 3

An extract of Alpinia galanga according to the invention was prepared as follows:

50 g dried root of Alpinia galanga was extracted with 500 ml of boiling acetone for 3 hours. This extraction was repeated with the same starting material using again 500 ml acetone in 3 hours. Thereafter the extract was filtrated and evaporated to dryness under vacuum. Thus, 2.1 g of an amber-coloured liquid extract was obtained suitable for the manufacture of tablets, hard gelatine capsules, ointment, nasal drops, etc.

Example 4

An extract of Alpinia galanga according to the invention was prepared as follows:

50 g dried root of Alpinia galanga was extracted with 500 ml of boiling ethyl-acetate for 3 hours. This extraction was repeated with the same starting material using again 500 ml ethyl-acetate in 3 hours. Thereafter the extract was filtrated and evaporated to dryness under vacuum. Thus, 1.4 g of an amber-coloured liquid extract was obtained suitable for the manufacture of tablets, hard gelatine capsules, ointment, nasal drops, etc.

Example 5

An extract of Alpinia galanga according to the invention was prepared as follows:

50 g dried root of Alpinia galanga was extracted with 500 ml of boiling hexane for 3 hours. This extraction was repeated with the same starting material using again 500 ml hexane in 3 hours. Thereafter the extract was filtrated and evaporated to dryness under vacuum. Thus, 1.8 g of an amber-coloured liquid extract was obtained suitable for the manufacture of tablets, hard gelatine capsules, ointment, nasal drops, etc.

Example 6

A distillate of Alpinia galanga according to the invention was prepared as follows:

Dried root of Alpinia galanga was steam-distilled. A golden-coloured liquid was obtained suitable for the manufacture of hard gelatine capsules, ointment, nasal drops, etc.

Example 7

An extract of Alpinia galanga according to the invention was formulated in a preparation for use as nasal drops or nasal spray, according to the following prescription:

For preparation of 100 g nasal spray, 1 mg/ml:

a) Extract of Alpinia galanga:	0.05 g
b) Cremophor RH 40, BASF:	2.00 g
c) Ethylenediamine tetraacetic acid, Fluka:	0.05 g
d) Benzalkoniumchloride, Sigma:	0.01 g
e) Sodium chloride, Merck:	0.89 g
f) Milli Q water, Millipore:	97.00 g

Procedure:

a) is dispersed in b) while heated to 37 °C on a water bath; c), d) and e) are added. After mixing, f) is added little by little under vigorous mixing.

A nasal spray formulation, prepared according to the above prescription, and using an extract of Alpinia galanga prepared as described in example 5, was tested by 4 volunteers. The nasal spray was reported to be effective against allergic rhinitis.

Example 8

An extract of Alpinia galanga according to the invention was formulated in an ointment preparation according to the following precription:

For preparation of 30 g ointment, 0,5 %:

a) Extract of Alpinia galanga:	0.3 g
b) Cremeol E-45, Århus Oliefabrik A/S:	19.5 g
c) Volatile Silicone VS72, Bionord A/S:	9.0 g
d) Cremeol HF-52 SPC, Århus Oliefabrik A/S:	1.2 g

Procedure:

d) is melted at approx. 100 °C; and b) is added under continuous heating and mixing. Then c) is added, and the mixture is cooled to room temperature. Finally a) is added, and the formulation is mixed. The formulation is filled on tubes, ointment jars or similar.

Ointment formulations, prepared according to the above precription, using extracts of Alpinia galanga prepared as described in Example 1 and Example 3, respectively, were tested by 5 volunteers. Both ointment preparations were reported to be effective against atopic eczema and psoriasis eczema, by alleviating eczema rash and itching.

Example 9

Study object

Four extracts of Alpinia galanga according to the invention and prepared as described in examples 1, 3, 4 and 5, hereafter correspondingly called Extract 1, 3, 4 and 5, respectively, were investigated in this study. After the preparation according to Example 1, Extract 1 is resolubilised in methanol, 10 % v/v hexane is added, and the mixture is filtrated and evaporated. This additional procedure is performed in order to remove starch, which may interfere with the intraveneous (i.v.) Passive Cutaneous Anaphylaxis (PCA) assay.

Study summary.

Background

The objective of the study was to evaluate the anti-allergic effect of the four extracts of Alpinia galanga in a well established assay for anti-allergic activity, the Passive Cutaneous Anaphylaxis (PCA) test.

Methods

Test substances (Extract 1, 3, and 5 ; 500 mg/kg), and vehicle (control) were given by peroral (p.o.) administration to a group of 3 Long Evans derived rats, passively sensitized 16 hours earlier by intradermal injection of reaginic (IgE) antiovalbumin serum (0.05 ml). Within 30 minutes after administration of the test substance, the animals were challenged i.v. with a mixture of ovalbumin (1 mg) and Evans Blue dye (5 mg) and sacrificed 30 minutes later. Inhibition of the resulting PCA blue coloured wheal indicates possible antiallergic activity.

A similar PCA test using i.v. administration of the test substances (Extract 1, 3, 4 and 5) and vehicle (control) was performed. The test substances were administered i.v. (20 mg/kg) to a group of 3 Long Evans derived rats passively sensitized 16 hours earlier by intradermal injection of reagenic (IgE) antiovalbumin serum (0.05 ml). Immediately after administration of the test substance, the animals were challenged i.v. with a mixture of ovalbumin (1 mg) and Evans Blue dye (5 mg) and sacrificed 30 minutes later.

Findings

The percent inhibition (mean) compared to the vehicle (control) of the PCA blue colored wheal for the groups treated with the test extracts in the assay using p.o. administration is shown in figure 1. The similar results obtained in the assay using i.v. administration is shown in figure 2.

In the assay using p.o. administration, all three extracts (Extract 1, 3 and 5) revealed a marked inhibition compared to the vehicle (control), as shown in figure 1. As shown in figure 2, the results from the assay using

i.v. administration revealed even stronger inhibition compared to the vehicle (control).

Interpretation

In this study it is clearly demonstrated that extracts from Alpinia galanga according to the invention and prepared as described in example 1, 3, 4 and 5, possess powerful anti-allergic activities. As it would normally be expected, the bioavailability seems to be slightly decreased when peroral administration is used instead of i.v. administration. However, the bioavailability in peroral administration might be considerably increased by formulating the extract with suitable carrier formulations or other pharmaceutical additives.

Example 10

Study object

An extract of Alpinia galanga, prepared according to example 3, hereafter correspondingly called Extract 3, was investigated in this study for inhibitory activity in three enzyme inhibition assays, Leukotriene C4 Synthetase, 5-Lipoxygenase and Phosphodiesterase-IV, respectively.

Study summary

Background

The objective of the study was to establish the activity of Extract 3 as a leukotriene inhibitor in the lipoxygenase pathway and as a phosphodiesterase-IV (PDE IV) inhibitor.

Leukotriene C4 (LTC4) synthetase and 5-lipoxygenase are enzymes involved in the lipoxygenase pathway. Leukotriene C4 (LTC4) synthetase is involved in the formation of LTC4 from LTA4. 5-Lipoxygenase catalyzes the oxidative metabo-

lism of arachidonic acid to 5-hydroxyeicosatetraoic acid (5-HETE), the initial reaction leading to formation of leukotrienes. Thus, taken together these assays may establish the degree of activity as well as a locus of action for agents which inhibit the formation of leukotrienes.

Phosphodiesterase type IV (PDE IV) catalyses the conversion of cAMP or cGMP to their respective monophosphate forms. PDE IV is insensitive to Ca^{2+}/calmodulin or cGMP regulation, exihibits a cAMP substrate dependence, and is inhibited by the specific inhibitor RO 20-1724. Since cyclic nucleotides are important second messengers in the cells of many tissues and organs, development of therapeutics that selectively target specific PDE isoforms is considered an important goal. PDE IV is believed to be the most important PDA isoform in bronchial relaxation, allergy and inflammation. Inhibitors for PDE IV are therefore considered valuable agents in the treatment of astma, allergy and inflammatory disease.

Methods

Leukotriene C4 synthetase assay

LTC4 synthase prepared as a crude fraction from guinea pig lung was used. The test compound, extract 3, was tested in duplicate at a concentration of 300 µg/ml. The test compound and/or vehicle was incubated with 12 µg enzyme, 0.3 µg LTA4 methyl ester, 0.2 % albumin (to stabilize the product) and 4.5 mM serine borate (to prevent conversion of LTC4 to LTD4) in phosphate buffer pH 7.8 for 30 minutes at 37 °C. The reaction was terminated by addition of ice-cold methanol. Formation of LTC4 was quantitated by RIA (radioimmunoassay). The result is used as an index of enzyme activity.

5-Lipoxygenase assay

A crude 5-lipoxygenase enzyme preparation from rat basophilic leukemia cells (RBL-1) was used. The test compound, extract 3, was tested in duplicate at a concentration of 9 µg/ml. The test compound and/or vehicle was pre-incubated with enzyme for 5 minutes in Tris buffer pH 7.2 at room temperature. The reaction was initiated by addition of 15 µM arachidonic acid as substrate and continued for an additional 8 minutes after which the reaction was terminated by addition of 70 mM citric acid. The formation of 5-HETE was quantitated by RIA.

Phosphodiesterase-IV assay

PDE IV partially purified from human U937 pronocytic cells was used. The test compound, extract 3, was tested in duplicate at a concentration of 30 µg/ml. Test compound and/or vehicle was incubated with 40 µg enzyme and 1 µg cAMP containing 0.01 µM [3H]cAMP in Tris buffer pH 7.5 for 20 minutes at 30oC. The reaction was terminated by boiling for 2 minutes and the resulting AMP was converted to adenosine by addition of 10 mg/ml snake venom nucleotidase and further incubation at 30oC for 10 minutes. Unhydrolyzed cAMP is bound to AGI-X2 resin, and remaining [3H]adenosine in the aqueous phase is quantitated by scintillation counting.

Findings

Compounds are considered active and the result significant if a >50 % inhibition is observed. Significant inhibitory activity of Extract 3 was observed versus all enzymes tested, see table 1.

TABLE 1

Enzyme inhibition assay	Concentration tested (µg/ml)	Percent inhibition
Leukotriene C4 synthetase	300	81 %
5-Lipoxygenase	9	53 %
Phosphodiesterase-IV	30	56 %

Interpretation

In this study it is clearly demonstrated that extracts of Alpinia Galanga according to the invention and prepared as described in example 3 (Extract 3) possess powerful leukotriene and phosphodiesterase-IV inhibitor activity. By inhibiting Leukotriene C4 synthetase as well as 5-lipoxygenase, Extract 3 plays a powerful role in the lipoxygenase pathway, inhibiting the formation of leukotrienes. As leukotrienes are important mediators of acute inflammation, including acute hypersensitivity, Extract 3 is considered to possess very promising properties in the treatment of diseases related to inflammation and hypersensitivity.

Furthermore, Extract 3 showed strong phosphodiesterase-IV (PDE IV) inhibitory activity. As PDE IV is believed to be the most important PDE isoform in bronchial relaxation, allergy and inflammation, inhibitors of PDA IV are considered very useful in the treatment of asthma, allergy and inflammatory diseases.

PATENT CLAIMS

1. An extract or concentrate of Alpinia galanga or Languas galanga containing:

a) 2-99,5 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 0,5-98 % essential oil of Alpinia galanga or Languas galanga or mixtures thereof.

2. An extract or concentrate of Alpinia galanga or Languas galanga containing:

a) 2-99,5 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 0,5-98 % of one or more compounds selected from the group consisting of 1,8-cineol, α-pinene, β-pinene, limonene, α-terpineol, terpen-4-ol, and trans-β-farnesene.

3. An extract or concentrate of Alpinia galanga or Languas galanga containing:

a) 2-99,5 % 1'-acetoxychavicol acetate;

b) 0,5-98 % of one or more compounds selected from the group consisting of 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol.

4. A pharmaceutical or food composition comprising:

a) 0,01-99,9% of an extract or concentrate of Alpinia galanga or Languas galanga according to any one of claims 1-3;

b) 0,1-99,99% of a pharmaceutically acceptable vehicle.

5. A pharmaceutical or food composition comprising:

a) 0,01-99,89 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 0,01-99,89 % essential oil of Alpinia galanga or Languas galanga or mixtures thereof;

c) 0,1-99,98 a pharmaceutically acceptable vehicle.

6. A pharmaceutical or food composition comprising:

a) 0,01-99,89 % of one or more compounds selected from the group consisting of 1'-acetoxychavicol acetate, 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hydroxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

b) 0,01-99,89 % of one or more compounds selected from the group consisting of 1,8-cineol, α-pinene, β-pinene, limonene, α-terpineol, terpen-4-ol, and trans-β-farnesene;

c) 0,1-99,98 % of a pharmaceutically acceptable vehicle.

7. A pharmaceutical or food composition comprising:

a) 0,01-99,89 % 1'-acetoxychavicol acetate;

b) 0,01-99,89 % of one or more compounds selected from the group consisting of 1'-acetoxyeugenol acetate, trans-p-coumaryl diacetate, coniferyl diacetate, 1'-hydroxychavicol acetate, 1'-hydroxychavicol, p-hy-

droxy-trans-cinnamaldehyd, p-methoxy-trans-cinnamylalkohol and 3,4-dimethoxy-trans-cinnamylalkohol;

c) 0,1-99,98% of a pharmaceutically acceptable vehicle.

8. A pharmaceutical or food composition comprising:

a) 0,01-99,89% of Alpinia galanga or Languas galanga or parts, extracts or components thereof or an extract or concentrate thereof according to any one of claims 1-3;

b) 0,01-99,89% of Zingiber officinale or parts, extracts or components thereof;

c) 0,1-99,98% of a pharmaceutically acceptable vehicle.

9. A pharmaceutical or food composition comprising:

a) 0,01-99,89% of Alpinia galanga or Languas galanga or parts, extracts or components thereof or an extract or concentrate thereof according to any one of claims 1-3;

b) 0,01-99,89% of γ-linolenic acid or eicosapentaenoic acid, optionally in the form of vegetable oil or fish oil;

c) 0,1-99,98% of a pharmaceutically acceptable vehicle.

10. The use of Alpinia galanga, Languas galanga or parts thereof or an extract or concentrate according to any one of claims 1-3 for preparing a medicament for immunomodulation.

11. The use of Alpinia galanga, Languas galanga or parts thereof or an extract according to any one of claims 1-3 for preparing a medicament for the suppression of hypersensitivity reactions.

12. The use according to claim 10 or 11 for preparing a medicament for the treatment or prevention of hypersensitivity diseases.

13. The use according to claim 10 or 11 for preparing a medicament for the treatment or prevention of IgE mediated allergic reactions and conditions.

14. The use according to claim 13 for preparing a medicament for the treatment or prevention of asthma.

15. The use according to claim 13 for preparing a medicament for the treatment or prevention of allergic rhinitis.

16. The use according to claim 13 for preparing a medicament for the treatment or prevention of atopic eczema.

17. The use according to claim 13 for preparing a medicament for the treatment or prevention of anaphylaxis.

18. The use according to claim 10 or 11 for preparing a medicament for the treatment or prevention of autoimmune disorders.

19. The use according to claim 18 for preparing a medicament for the treatment or prevention of Crohn's disease or ulcerative colitis.

20. The use according to claim 18 for preparing a medicament for the treatment or prevention of rheumatoid arthritis.

21. The use according to claim 18 for preparing a medicament for the treatment or prevention of psoriasis.

22. The use of Alpinia galanga, Languas galanga or parts thereof or an extract according to any one of claims 1-3 for the alleviation of pain.

23. A method for the treatment or prevention of a hypersensitivity disease in an individual, which comprises administering Alpinia galanga, Languas galanga or parts

thereof or an extract according to any one of claims 1-3 or a pharmaceutical composition according to any one of claims 4-9 to said individual.

24. A method for the treatment or prevention of an autoimmune disorder in an individual, which comprises administering Alpinia galanga, Languas galanga or parts thereof or an extract according to any one of claims 1-3 or a pharmaceutical composition according to any one of claims 4-9 to said individual.

25. A method for the treatment or prevention of an IgE mediated allergic reaction or condition in an individual, which comprises administering Alpinia galanga, Languas galanga or parts thereof or an extract according to any one of claims 1-3 or a pharmaceutical composition according to any one of claims 4-9 to said individual.

26. A method for the alleviation of pain in an individual, which comprises administering Alpinia galanga, Languas galanga or parts thereof or an extract according to any one of claims 1-3 or a pharmaceutical composition according to any one of claims 4-9 to said individual.

27. A method of preparing an extract of Alpinia galanga, which comprises distilling fresh or dried Alpinia galanga or parts thereof, preferably the rhizome, and/or extracting said plant material with an extraction agent comprising an organic solvent or water or mixtures thereof and subsequently, if necessary, removing the extraction agent to obtain an extract suitable for utilisation.

28. A method according to claim 22, wherein said solvent is an organic solvent selected from the group consisting of acetone, methyl ethyl ketone, methyl acetate, ethyl acetate and lower alkanols having 1 to 4 carbon atoms, pentan, hexan and heptan or mixtures thereof.

29. A method according to claim 22 or 23, wherein the extract is further subjected to liquid-liquid extraction for the removal or concentration of certain constituents.

30. An extract prepared according to the method of any one of claims 22-24.